REMARKS

Applicant submits this Preliminary Amendment in association with a Request for Continued Examination (RCE) on said application. Applicant respectfully requests that the claim amendments made herein be entered in accordance with the filing of the RCE.

In the most recent Office Action claims 13-17, and 29-41 were rejected. Applicant currently presents amended claims 13-17, 29-41 that Applicant feels are now in condition for allowance, and notice to that effect is respectfully requested. Most notably, claim 13 has been amended to state, in element (b) of said claim, that the oligonucleotide "consists of a single stranded DNA oligonucleotide that forms a DNA duplex." Support for such amendment can be found throughout the application and is depicted in Figures 1A – 1D. A similar amendment was made to claim 33. Applicant also made an amendment to several claims in response to the 35 USC § 112 rejection addressed below.

In re Crish

The Advisory Action January 9, 2006 notes that the request for reconsideration filed by Applicant was considered but did not place the application in condition for allowance because the Examiner suggested that the use of the terms "consisting of" and "comprising" in a single claim must be considered in light of the recent Federal Circuit decision *In re Crish*, 393 F3d 1253 (Fed Cir 2004).

Applicant respectfully submits that the holding of *Crish* does not affect the present claims as amended. Specifically, the Court in *Crish* states that "[t]he reasonable interpretation of the claims containing both of the terms 'comprising' and 'consists' is that the term 'consists' limits the 'said portion' language to the subsequently recited numbered nucleotides, but the earlier term 'comprising' means that the claim can include **that portion plus other nucleotides.**" (*Id* at 1257) (Emphasis added). In the present claims, while it may be arguable that the earlier term "comprising" means that the claim can include DNA oligonucleotides plus other oligonucleotides, the relevant prior art does not contemplate the use of DNA oligonucleotides plus other oligonucleotides. As argued hereinbelow, Basczynski is limited to RNA-DNA hybrid oligonucleotides, and does not contemplate the use of DNA oligonucleotides. As such, Applicant respectfully submits that the holding of *In re Crish* does not change the scope of the amended claims in such a way that they can be interpreted to fall within the disclosure of Basczynski, either under 35 USC §§ 102 or 103.

A. Claim Rejections – 35 U.S.C. § 112

Claims 33-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of a series of antecedent basis problems. Specifically, Examiner finds that it is unclear which duplex DNA is a plasmid in the concluding wherein clause of claim 33.

To correct the rejection based on antecedent basis, Applicant has currently amended claims 13, 30-33, 37, and 39-41 to clarify that the duplex DNA that is being referred to is the "duplex DNA comprising the target sequence." The claims as amended contain no new matter.

In view of the amendments, Applicants believe that this grounds for rejection has been adequately traversed. Applicant respectfully requests that Examiner consider the amended claims, and withdraw this rejection.

B. Claim Rejections – 35 U.S.C. § 103

The Examiner states that claims 13-17 and 29-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamashita et al. (EP 718, 404) in view of Baszcynski et al (U.S. 6,528,700).

I. Yamashitaand Baszcynski

Examiner states that Yamashita teaches oligonucleotides that are approximately 22-24 nucleotides in length; an oligonucleotide with a single 3' and 5' end; the LacZ gene, which is linked to a promoter that can be expressed; and a duplex DNA that is a plasmid DNA. Examiner states that Yamashita does not teach the use of a plant cell extract or the oligonucleotide of claim 29.

Examiner states that Baszcynski teaches an oligonucleotide with a single 3' and 5' end; a double stranded DNA plasmid comprising the AHAS gene under control of the ubiquitin promoter; a self complementary oligonucleotide with at least 5 bases that are base paired; and an oligonucleotide which comprises a "duplex."

Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use a plant cell extract as taught by Baszcynski in the composition of Yamashita.

II. Applicant's Comments Regarding Examiner's 103(a) Rejection.

Applicant has amended the transitional language of the claims to indicate that the present invention is drawn to the use of oligonucleotides consisting only of DNA. Specifically, the transitional phrase in element (b) of each of claims 13 and 33 has been changed from "comprising" to "consists of" to make clear that Applicant claims only the use DNA oligonucleotides.

Applicant believes that in light of the above amendments to the claims, Examiner's rejections are moot and allowance of the amended claims is respectfully requested. In addition, for the purposes of providing a complete response, Applicant addresses each of the Examiner's specific grounds for rejection based on 35 U.S.C. 103(a).

The three essential criteria that must be established to substantiate an obviousness rejection are: (1) the reference must teach or suggest *all* the claim limitations; (2) there *must* be a reasonable expectation of success; and (3) there *must* be some suggestion or

motivation in the reference themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings. There must be something in the prior art that suggested the combination of these particular prior art compositions and processes other than the hindsight gained from knowing that the inventor chose to combine these particular things in this particular way. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051 (Fed. Cir. 1988).

(1) The cited references do not teach or suggest each and every element of the claimed invention. *In re Royka*, 490 F.2d 981 (CCPA 1974).

Examiner states that Yamashita recognizes the equivalence of plants and other cell types, noting that host cells can include "bacteria such as *E. Coli* and *Bacillus subtilis*, yeasts, fungi, plant cells, and animal cells." Examiner also finds that an ordinary practitioner would have been motivated by Yamashita to use other cell free extracts from sources which would function in gene correction, including equivalent extracts from plants.

As a matter of contradistinction, Applicant points out that Yamashita teaches the use of an artificial, cell-free, in vitro system for performing site-directed mutagenesis. The cell-free system of Yamashita contains no other components of the cellular milieu as one would find in a cellular extract. In addition, Yamashita teaches the use of cellular hosts not for gene correction as Examiner suggests, but purely for the propagation/selection/isolation of clones that contain the modified gene, after performing the mutagenesis reaction. This aspect of the Yamashita disclosure simply recognizes that certain cells can be used for the continued propagation of an artificial DNA construct, and does not implicate or suggest equivalence of any cell type for any other purpose. In fact, those of ordinary skill in the art readily recognize that even for the limited purpose of propagation and selection, cell types differ in their usefulness. Moreover, Yamashita, through its teachings would not suggest or motivate one of ordinary skill to perform the exchange reaction using the extract from any cell type.

Examiner finds that Baszcynksi motivates the use of plant extracts since it teaches that "compositions and methods for targeted gene correction, conversion, or modification in plants are provided." Examiner then concludes that an ordinary practitioner would have been motivated by Baszcynski to use plants for modification since Baszcynski teaches *in vitro* plant cell extracts and ways to gene correct plants, while Yamashita recognizes the equivalence and use of other cell free extracts.

As stated previously, Applicant suggests it is erroneous to state that Yamashita recognizes the alleged equivalence of various cell types for anything other than possibly the limited purpose of propagation and/or selection. Furthermore, nothing in Yamashita would suggest or motivate one of ordinary skill to use a cellular extract in view of the fact that it teaches only the use of a cell-free system involving a single enzyme. More to the point, to the extent that Yamashita teaches that plant cells may be the equivalent to other cells for performing recombination, it is in error. Those of ordinary skill in the art widely recognize that plant cells are particularly adept at degrading DNA oligonucleotides. In fact, this distinction is alluded to in the Baszcynski reference. (See Col 5, line 32-38 of Baszcynski that reads, "the hybrid molecule presents no impediment to pairing , and protects the vector from exonucleolytic degradation.").

While Applicant recognizes that Baszcynski shows a plant or plant extract, Baszcynski does not, however, teach, suggest, or motivate the use of an oligonucleotide consisting only of DNA. Instead, Baszcynski expressly teaches the use of RNA-DNA hybrid oligonucleotides and teaches away from the use of an oligonucleotide consisting solely of DNA as presently claimed. (See, for example, Col 2, lines 52-55 of Baszcynski that reads, "homologous pairing between the chimeric oligonucleotide and the plant's target sequence and the strand transfer process are enhanced by the modified RNA residues." See also, Col 5, lines 29-31, that reads, "the design of the chimeric oligonucleotide, or vector, is based on the discovery that RNA-DNA hybrids are highly active in homologous pairing reactions in vitro.").

(2) There is no suggestion or motivation in the prior art references or in the knowledge generally available to one or ordinary skill in the art to modify or combine reference teachings in the manner proposed by the Examiner.

The mere presence of an element of the invention in prior art references without more (i.e. the suggestion or motivation to combine and the reasonable likelihood of success) is not sufficient to maintain a prima facie case of obviousness. The mere fact that references can be combined or modified does not render the combination obvious unless prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). Furthermore, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). However, Applicant contends that there is also nothing in the cited prior art that would even motivate one of ordinary skill in the art at the time of the invention to combine or modify the teachings.

First, Yamashita does not teach or suggest, let alone motivate one of ordinary skill in the art to use a single stranded, self-complementary DNA oligonucleotide to perform mutagenesis or recombination. Furthermore, Yamashita does not teach, suggest or motivate one of ordinary skill in the art to use a cellular extract or a plant extract. In addition, at the time of the invention Baszcynski expressly taught away from the use of an oligonucleotide consisting only of DNA. Specifically, Baszcynski teaches that RNA-DNA chimeric oligonucleotides "are highly active in homologous pairing reactions..."; "protect the vector from exonucleolytic degradation." (Col 5, lines 30-34). Moreover, Baszcynski further emphasizes that the "vector is activated for recombination by the incorporation of RNA residues...", and homologous recombination is "enhanced by the modified RNA residues." (Col 5, lines 30-39).

In light of the discussion provided above, Applicant believes that there was no suggestion to one of ordinary skill in the art to modify or combine the teachings of Yamashita and Basczynski. Furthermore, Applicant believes that even assuming, *arguendo*, that there was some suggestion to combine the teachings, the knowledge generally available at the time of the invention did not rise to the necessary level to motivate a combination of the references because, (1) the Yamashita reference does not teach the use of any of Applicant's claimed features; and (2) the Baszcynski reference expressly teaches away from the use of an oligonucleotide consisting only of DNA.

(3) Based on the uncertainty of the chemical and biological sciences, and the knowledge of one of ordinary skill at the time of the invention, a conclusion that the prior art provided a reasonable expectation of success at the time of the invention cannot be factually supported.

Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Providing evidence of a reasonable expectation of success is difficult where, as here, the claimed invention involves the application of an unpredictable technology. *Genetech, Inc. v. Novo Nordisk*, 108 F.3d 1361 (Fed. Cir. 1997). Obviousness and expectation of success are evaluated from the perspective of a person having ordinary skill in the art at the time of the invention. In *Velander v. Garner*, 348 F.3d 1359 (Fed. Cir. 2003), the court stated that there must be (i) substantial evidence that (ii) supports the conclusion that it was more probable than not that, as of the critical date, one of ordinary skill in the art would have had a reasonable expectation of success.

The Applicant maintains that based on the uncertainty of the biochemical arts, and in view of the limited teachings of Yamashita, and the contrary teachings of Baszcynski, a person of ordinary skill in the art would not have a reasonable expectation of success.

Applicant honestly believes that this paper represents a complete response to Examiner's comments, and in view of the presented arguments and amendments, it is respectfully submitted that the application is now in condition for allowance and notification to this effect is respectfully requested.

CONCLUSION

The foregoing is believed to be fully responsive to this office action. The embodiments presented are believed to be allowable over the prior art of record. Consideration and allowance of the claims is respectfully requested.

If the Examiner believes that a telephone conference with Applicants' attorneys would be advantageous to the disposition of this case, the Examiner is cordially requested to telephone the undersigned. If the Examiner has any questions in connection with this paper, or otherwise if it would facilitate the examination of this application, please call the undersigned at the telephone number below.

99689-00019

Applicant has paid a one-month extension of time fee of $60.00 with response filed on December 16, 2005. Therefore, Applicant requests that a three-month extension of time fee be charged in the amount of **$510.00** to **Deposit Account No. 50-3570**. In the event that any fee has been inadvertently overlooked and is required, the Commissioner is hereby authorized to charge any required fee or credit any overpayment to **Deposit Account No. 50-3570.**

Respectfully submitted,

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